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SANDOZ INC
506 CARNEFIE CENTER
PRINCETON, NJ 08540

EXAMINER	
LEAVITT, MARIA GOMEZ	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/568,337	WINDISCH ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06-10-2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20 and 22-43* is/are pending in the application.

4a) Of the above claim(s) *9,18 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 10-17, 19, 20, 22-28 and 30-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03-18-2009 has been entered.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Status of claims. Claims 1-20, 22-43 are currently pending. Claims 9, 18, and 29 were previously withdrawn from further consideration pursuant to 37 CFR1.14(b) as being drawn to nonelected species. Claims 10 and 43 have been amended by Applicants' amendment filed on 03-10-2009.
3. Therefore, claims 1-8, 10-17, 19, 20, 22-28 and 30-43 are currently under examination to which the following grounds of rejection are applicable.

Response to arguments

Withdrawn Rejections/Objections in response to Applicants' arguments or amendments

Claim objection

In view of Applicant's amendment of claims 10, objection to claim 10 has been withdrawn.

In view of the withdrawn rejection, applicant's arguments are rendered moot.

Claim Rejections - 35 USC § 112- First paragraph- New Matter

In view of Applicants' amendment of claim 43, rejection of claim 43 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement-New matter-, has been withdrawn.

A review of the specification as filed reveals specific disclosure for the nucleotide sequence of the expression vector cassette used in the rhIFNα2b expression plasmid pMG414 (807 bps) comprising the following four regions directly joined to one another: the gac promoter and RBS, the gac signal sequence coding region, the synthetic gene for rhIFNα2b including the TAA stop codon and the 3' cloning linker (page 23, paragraphs 2-3; also see post filing art by inventors Knauseder et al., 2007, JP 2007501623, Accession DJ004039) .

In view of the withdrawn rejection, applicant's arguments are rendered moot.

Rejections/Objections maintained n response to Applicant arguments or amendments:

Nature of the invention

The present invention is broadly drawn to an expression vector comprising a polynucleotide encoding a fusion protein for expression of a heterologous protein e.g. independent claim 1, a host cell (e.g., *E. Coli*) comprising said vector, e.g., independent claim 10, and a method for production of the recombinant protein in said host cell e.g., independent claim 20, the vector comprising a **signal sequence of gac gene** (glutaryl 7-aminocephalosporanic acid (ACA) acylase) of *Pseudomonas diminuta* and a gene encoding a polypeptide of interest. Claims 6, 15 and 26 limit the invention to the polynucleotide encoding a signal sequence of *Pseudomonas diminuta* comprising the amino acid sequence of **SEQ ID No. 2**. Moreover, claims 8, 15 and 28 further limit the invention to a vector comprising a polynucleotide comprising the

promoter and ribosomal biding site of the gac gene of Pseudomonas *diminuta* comprising the nucleotide sequence of **SEQ ID No. 5**. The specification teaches that the heterologous polypeptide rhIFNα2b (recombinant human Interferon-α2b) is produced in the *Escherichia coli* K-12 strain W3110 transformed with a plasmid containing an optimized synthetic gene coding for rhIFNα2b. Moreover, the rhIFNα2b is produced under the control of the promoter and the Ribosome Binding Site (RBS) of gac gene of *Pseudomonas diminuta* CCM 3987 by fermentation of recombinant *E. coli* K-12. RhIFNα2b is expressed as an N-terminal fusion protein with the signal sequence from the same (gac) gene, directing the protein to the periplasm with concurrent processing (cleaving off) of the signal sequence. It is noticed that the art at the time the invention was made teaches that heterologous proteins expressed in *E. coil* are secreted to the periplasm if they possess a N-terminal signal sequence (French et al., 1996, *Enz and Microb Tech* pp. 332-338, of record). Therefore, the fermentation process directly yields mature rhIFNα2b with a primary sequence identical to that of naturally occurring human Interferon α2b (p. 15, Example 1). Additionally, the instant invention contemplates the production of any recombinant polypeptide of interest other than gac gene of *Pseudomonas diminuta* in a prokaryotic host cell (p. 3, paragraph 3).

Claim Rejections - 35 USC § 103

Claims 1-3, 6-8, 10-12, 15-17, 19, 22-23, 26-28, 30-43 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Peleg et al., (WO 03/004599 A2, Date of Publication 16-Jan-2003) in view or Matsuda et al. (J. of Bacteriology, 1985, p. 1222-1228), Ishii et al., (Journal of Fermentation and Bioengineering , 1994, pp. 591-597) or Kim et al., (Biotechnology Letters, 2001, pp. 1067-1071).

Peleg et al., discloses a method for the production and purification of a fusion polypeptide in *E. Coli*, the method comprising introducing into the bacteria an expression construct encoding the fusion polypeptide which comprises a TAT-derived peptide and a protein of interest, whereby the TAT derived peptide serves for transport of the fusion polypeptide from the bacterial cytoplasm to the periplasm (Abstract). Peleg clearly discloses "that transport of proteins through the inner membrane to the periplasmic space requires the inclusion of a signal peptide" (p. 3, lines 8-10). Peleg described a "signal sequence" as a "short (e.g., 15-40) amino acid sequences, which allows proteins to transport through the bacterial inner membrane of the periplasm" (p. 21, lines 23-26). In addition to the virally-derived TAT lead sequence, Peleg et al., discloses the structure and functionality of other lead sequences including bacterial signal peptides well known in the art from mycoplasmas, other gram positive bacteria and *E. coli* (p. 26, lines 27-30 bridging to p. 27, lines 1-19). In preferred embodiments, Peleg et al., teaches that the vector comprises a polynucleotide harboring a polylinker sequence being operably linked to the signal sequence and **a prokaryotic promoter** being operably linked to the periplasmic targeting sequence of TAT (p. 11, lines 12-18; p. 20, line 14-17). Peleg et al., teaches at page 25, lines 4-14, plasmids and high copy plasmids such as plasmids from the pUC series (line 5). Indeed, Peleg et al., exemplifies a construct wherein a bacterial signal sequence in frame with the TAT-derived peptide and protein of interest provides for cleavage of the signal sequence and the TAT-derived sequence, and provides a mature, properly folded and functional protein, readily isolable and purifiable (p. 7, lines 12-16; p. 21, lines 1-5). Note that the process of fermentation as encompassed by claim 32 comprising a culture medium with a substrate for more than about 90% of the cultivation time at a substrate concentration lower than the saturation constant of the

substrate, accompanied by high levels of dissolved oxygen concentration, which is further accompanied by a steadily decreasing specific growth rate of the bacterial host cells is intrinsic to the process of fermentation in absence of evidence to the contrary)**(Current claims 1-3, 7, 10-12, 19 and 42, in part)**.

In relation to the fermentation process, Peleg et al., discloses a multi stage fermentation process comprising a shake-flask step, a pre-culture step and a final culture step (p. 43, lines 5-21). Conditions of fermentation for the production of the polypeptide of interest are disclosed at pages 40-45, including initial incubation temperature at 30°C for 14 hours (p. 41, line 6), fermentation medium containing carbohydrates, e.g., glucose, fermentation feeding maintained at 4 g/L (p. 43, lines 15-18; p. 43, line 25-26), dissolved oxygen measured to be 30% and maintained by increasing agitation (p. 43, lines 26-29), pH maintained at 7.2 (p. 43, line 22). At page 14, lines 14-30, Peleg et al., discloses a list of proteins including **interferon** (lines 26) expressed as a fusion polypeptide in the periplasmic space where processing occurs, providing the mature protein for isolation (p. 42, lines 25-27) **(Current claims 20, 22-25, 30-40, 41 and 43, in part)**

Peleg et al does not disclose a promoter, ribosomal binding site (RBS) and signal sequence of the gac gene of *Pseudomonas diminuta.*

However, at the time the invention was made, Matsuda et al. teaches the molecular cloning and structure of the the nucleotide sequence of the glutaryl (GL) 7-ACA acylase gene from *Pseudomonas sp.* GK16 comprising a nucleotide sequence encoding a 29 amino acids immediately upstream from the small subunit, said 29 aa sequence is disclosed as a signal peptide because of its structure (p. 1226, col. 1 and 2, Fig. 5). Moreover, Matsuda et al. teaches

that acylase activity was found in periplasm in the *E .coli* clone, corresponding to previous observations that the enzyme appeared to be periplasmic (p. 1226, col. 1 and 2, Fig. 5). Thus Matsuda et al. clearly teaches that the GL 7-ACA acylase from Pseudomonas sp. GK16 is transported to the periplasmic space in *E. coli* . Note that the signal sequence of 29 aa residues of the gac gene product of Matsuda comprises the peptide sequence of **SEQ ID NO: 2** of 27 aa residues (i.e., signal peptide) of the invention. Also note that the promoter region of the GL 7-ACA acylase gene as disclosed in Fig. 5, at page 1226 of Matsuda, comprises the same nucleotide sequence as the polynucleotide of **SEQ ID NO. 5** of the invention said gac promoter sequence comprising the putative ribosomal biding site 5' –GACG- 3', which is indicated by a box in Fig. 5. Similarly, Kim et al., discloses the gene coding for GL 7-ACA acylase from *Pseudomona diminuta* KAC-1 comprising a promoter with a RBS and a signal sequence comprising both SEQ ID No. 5 and SEQ ID NO. 2, respectively, as claimed in the instant invention. Likewise, Ishii et al., teaches the GL 7-ACA acylase from *Pseudomona* strain C427 comprising a 27 amino acid signal peptide immediately upstream from the small subunit (p. 592, Fig. 2). Moreover, Ishii et al., discloses that a proportion of active acylase is secreted into the periplasm in *E. coli* and the remainder is retained in the cytoplasm. Additionally, Ishii et al. teaches that the amount of precursor protein accumulated in the cytoplasm is greatly reduced when the plasmids for the acylase lacking the signal sequence are expressed (abstract), clearly indicating that in systems of high expression in *E. coli,* the signal sequence was required for translocation to the periplasmic space of *E. coli* and that without the signal sequence, active acylase accumulates in the cytosol. (**Current claims 6, 8, 15, 17, 26, 27 and 28**).

Therefore, in view of the benefits of producing and isolating a desired heterologous protein by using a recombinant fusion protein comprising a signal peptide and the protein of interest, whereby the effective periplasmic targeting sequencing transports the fusion polypeptide form the bacterial cytoplasm to the periplasm as taught by Peleg et al., it would have been *prima facie* obvious for one of ordinary skill in the art, as a matter of design of choice, to modify the fusion protein to introduce into the expression vector a polynucleotide encoding the signal peptide of the gac gene to secrete the heterologous protein into the periplasm of *E. coli*, particularly because Matsuda et al. Ishii et al., and Kim et al., suggest and teach the signal sequence of the gac gene of Pseudomona sp. GK16 or *Pseudomona diminuta* or *Pseudomona* sp. C427 comprising the instantly claimed signal sequence of the gac gene of Pseudomona diminuta which is required for translocation and secretion into the periplasm in *E. coli*. Moreover, it would have been *prima facie* obvious to replace the prokaryotic promoter being operably linked to the periplasmic targeting sequence of TAT as taught by Peleg to include the promoter of *Pseudomona diminuta* comprising the RBS in an attempt to provide improved transcriptional and translational regulatory systems in the expression vector of Peleg. The manipulation of previously identified DNA fragments, cell transformation systems and fermentation conditions for *E. coli* is within the ordinary level of skill in the art of molecular biology. Thus it would *have been obvious* to a person of ordinary skill in the art to try the he signal sequence and promoter comprising the RBS of the gac gene of *Pseudomonas diminuta* in an attempt to provide an improved formulation of the expression vector of Peleg, as a person with ordinary skill has a good reason to pursue known options within his technical grasp.

Reply to applicant arguments as they relate to rejection of claims 1-3, 6-8, 10-12, 15-17, 19, 22-23, 26-28, 30-43 under 35 USC § 103

Please, note that Applicants' remarks of 03-10-2009, to the extent that they did not rely upon the proposed amendments, were already addressed in the office action of 04-01-2009. Since Applicants have not provided essentially new arguments in addition to the ones already discussed at pages 3-5 of the office action of 04-01-2009, the Examiner refers Applicants to the reasons already of record as set for in the action of 04-01-2009.

Claims 4, 5, 13, 14, 24 and 25 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Peleg et al., (WO 03/004599 A2, Date of Publication 16-Jan-2003) in view or Matsuda et al. (J. of Bacteriology, 1985, p. 1222-1228), Ishii et al., (Journal of Fermentation and Bioengineering , 1994, pp. 591-597) or Kim et al., (Biotechnology Letters, 2001, pp. 1067-1071) as applied to claims 1-3, 6-8, 10-12, 15-17, 19, 22-23, 26-28, 30-43 above and further in view of Kwon et al., WO 01/057217, Date of publication 9 August 2001).

The combined teachings of Peleg, Matsuda, Ishii and Kim are outlined in the paragraphs above. The combined disclosure of Peleg, Matsuda, Ishii and Kim fails to teach a vector encoding a human interferon alpha in the fusion protein.

However, at the time the invention was made, Kwon et al., teaches expression vectors in the form of fusion protein which carry a signal peptide attached to their N-terminal for the secretive production of hIFNα subtypes 2a and 2b (p. 1, lines 6-13; p. 2, lines 27-28; p.3, lines 23-27). Moreover, Kwon et al., successfully exemplified secretion of interferon alpha 2A or 2B

in *E. coli* transformants into the periplasm at high productivity (p. 8, lines 1-2) (**Current claims 4, 5, 13, 14, 24 and 25**).

Therefore, in view of the benefits of producing and isolating a desired protein by using a recombinant fusion protein comprising a signal peptide and the protein of interest, whereby the effective periplasmic targeting sequencing transports the fusion polypeptide form the bacterial cytoplasm to the periplasm as taught by Peleg et al., it would have been *prima facie* obvious for one of ordinary skill in the art, as a matter of design of choice, to modify the fusion protein to introduce into the expression vector a polynucleotide encoding the signal peptide of the gac gene to secrete the heterologous protein into the periplasm of *E. coli*, particularly because and Matsuda et al. Ishii et al., and Kim et al., teach the signal sequence of the gac gene of Pseudomona sp. GK16 or *Pseudomona diminuta* or *Pseudomona* sp. C427 comprising the instantly claimed signal sequence of the gac gene of Pseudomona diminuta which is required for translocation and secretion into the periplasm in *E. coli*. Moreover, it would have been *prima facie* obvious for one of ordinary skill in the art, to generate an expression vector as a fusion protein comprising a polynucleotide sequence coding the human interferon alpha 2A or 2B for secretive production, particularly because Kwon et al., successfully exemplified secretion of interferon alpha 2A or 2B in *E. coli* transformants into the periplasm under a leading sequence at high productivity. The manipulation of previously identified DNA fragments, cell transformation systems and fermentation conditions for *E. coli* is within the ordinary level of skill in the art of molecular biology. One of ordinary skill in the art at the time the invention was made would had been motivated to combine the disclosure of Peleg Matsuda, Ishii, Kim and

Kwon to improve efficient production of mature interferon alpha 2A and 2B proteins in pure form in a high yield with a reasonable expectation of success.

Reply to applicant arguments as they relate to rejection of claims 4, 5, 13, 14, 24 and 25 under 35 USC § 103

Please, note that Applicants' remarks of 03-10-2009, to the extent that they did not rely upon the proposed amendments, were already addressed in the office action of 04-01-2009. Since Applicants have not provided new arguments in addition to the ones already discussed at pages 3-5 of the office action of 04-01-2009, the Examiner refers Applicants to the reasons already of record as set for in the action of 04-01-2009.

Claim Rejections - 35 USC § 112- Second Paragraph

Claims 16, 27, 42 and 43 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language.

Claims 16 and 27 recite "said vector further comprises a second polynucleotide … wherein the second polynucleotide is operatively linked to the polynucleotide encoding the fusion protein". It is unclear whether the second polynucleotide operatively linked to the polynucleotide encoding the fusion protein is expressed from the promoter of the polynucleotide encoding the fusion protein, from its own promoter or the first and second polynucleotides are operationally linked in a different way. Thus, claims 16 and 27 embrace several embodiments and hence, it is unclear what its metes and bounds are. It would be remedial to amend the claim language to clearly delineate between the different possibilities.

Claims 42 and 43, subparts b) recite "second polynucleotide comprising the promoter region and the ribosomal binding site of the gac gene of Pseudomonas diminuta, wherein the

second polynucleotide is operatively linked to the first polynucleotide encoding the fusion protein comprising the signal sequence and the polypeptide of interest" . It is unclear whether the second polynucleotide operatively linked to the polynucleotide encoding the fusion protein is expressed from the promoter of a) a first polynucleotide encoding the fusion protein, b) from its own promoter or both a) and b) are operationally linked in a different way. Thus, claims 42 and 43 embrace several embodiments and hence, it is unclear what its metes and bounds are. It would be remedial to amend the claim language to clearly delineate between the different possibilities.

Reply to applicant arguments as they relate to rejection of claims 16, 27, 42 and 43 under - 35 USC § 112- Second Paragraph

At page 18 of the remarks filed on 03-10-2009, Applicants essentially argue that claims 16, 27, 42 and 43 are not indefinite because the claims clearly recite a unique promoter, i.e., the gac promoter. Moreover, Applicants allege that support for the limitations recited in the claims is disclosed in the specification at pages 6-8. The above arguments have been fully considered but deemed unpersuasive.

The fact that there is a unique promoter recited in the claims is not disputed. As stated in the paragraph above, claims 16, 27, 42 and 43 are indefinite as they are directed to different possibilities in relation to how the first polynucleotide (e.g., gac signal sequence and the polypeptide of interest) and second polynucleotide (e.g., gac promoter comprising a ribosomal binding site) are operably linked. The specification at page 6, paragraphs 4-5, merely describes preferred embodiments wherein the polynucleotide encoding the gac signal sequence and the polypeptide of interest further comprises a second polynucleotide comprising a gac promoter and a ribosomal binding site operably linked to the gac signal sequence. As the claims embrace

several embodiments in relation to how the claimed polynucleotides are functionally linked, the meaning and the metes and bounds of the claim as whole are unclear.

New grounds of objection/rejection

Claim Objections

Claims 6, 8, 15, 17, 26 and 28 are objected to for the inclusion of the nucleotide sequences identified as SEQ ID NO: 2 (e.g., claims 6, 15 and 26) and SEQ ID NO:5 (e.g., claims 8, 15 and 28) in parenthesis. Sequence identifiers are the best description of the claimed sequence and thus should not be recited parenthetically.

Furthermore, claims 6, 8, 15, 17, 26 and 28 are objected to because of the recitation of both, the SEQ No identifier in parenthesis and the description of the nucleotide sequence. Recitation of just the SEQ No. would obviate the redundancy.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8, 10-17, 19, 20, 22-28 and 30-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 10, 20, 42 and 43 are indefinite in the recitation of the phrase "such as" because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claims 2-8, 9-17, 19, 22-28, and 30-41 are indefinite insofar as they depend directly or indirectly from claims 1, 10 and 20.

Additionally, claim 42 is indefinite in the reciting "the signal sequence" in line 3, "the gac gene" in line 4, "the promoter region" and "the ribosomal binding site" in line 10. There is no antecedent basis for "the signal sequence", "the gac gene" ,"the promoter region" and "the ribosomal binding site" in the claim. Therefore, the metes and bounds of "the signal sequence", "the gac gene", "the promoter region" and "the ribosomal binding site" are indefinite.

Additionally, claim 42 is indefinite in the reciting "wherein the host cell is stably transformed by the expression vector" A review of the specification as filed reveals no specific disclosure of stably transfection of host cell by an expression vector in the establishment of the recombinant cell line. What the specification does disclose regarding establishment of the recombinant cell line is that the expression plasmid pMG414 is introduced into the host strain ATCC PTA-3132 by electroporation (¶ [0128] of the published application), the creation of a Working Cell Bank and the fermentation process to express rhIFNα2B by growing the strain E. coli K-12 W3110 obtainable from the Working Cell Bank (¶ [0139] of the published application). Therefore, it is unclear whether the phrase "wherein the host cell is stably transformed by the expression vector" refers to transformant host that have lost the plasmid overtime (e.g., kanamycin-selectable plasmids vectors are more stable than Ampicilim resistant plasmids), integration of the plasmid vectors into the host chromosome, e.g., by homologous recombination, stability of the host carrying the recombinant plasmid, regulatable stable expression stability of the expression vector and others. Thus, claim 42 embraces several embodiments and hence, it is unclear what its metes and bounds are. It would be remedial to

amend the claim language to clearly delineate between the different possibilities.

Furthermore, claim 43 is indefinite in the reciting "the signal sequence" in line 4, "the promoter region" ,"the ribosomal binding site" and "the gac gene" in line 5. There is no antecedent basis for "the signal sequence", "the ribosomal binding site" and "the gac gene" in the claim. Therefore, the metes and bounds of "the signal sequence", "the ribosomal binding site" and "the gac gene" are indefinite.

Conclusion

Claims 1-8, 10-17, 19, 20, 22-28 and 30-43 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

/Maria Leavitt/

Maria Leavitt, PhD
Examiner, Art Unit 1633